Remarks

Claims 12-16, 30-41 and 50-66 are pending in this application. No claim amendments are made in this paper. Applicant respectfully submits that all of the pending claims are allowable for the following reasons.

Response to Claims Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 12-16, 30-41 and 50-66 as obvious over U.S. Patent No. 5,120,758 to Satoh ("Satoh") in view of U.S. Patent No. 5,990,147 to Aslanian ("Aslanian"). Applicant respectfully traverses this rejection.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To establish a case of *prima facie* obviousness the Examiner must show that: (1) the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed methods; and (2) that those of ordinary skill would have a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2143; *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). These criteria must be satisfied with factual and objective evidence found in the prior art; an examiner's conclusory statements cannot form a basis for a *prima facie* case of obviousness. *See In re Sang-Su Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002). Applicant respectfully submits that the Examiner has not presented factual and objective evidence to support her case of *prima facie* obviousness.

First, the Examiner has failed to show that the prior art contains any suggestion to carry out the claimed methods. The Examiner contends that because Satoh teaches formulations comprising a lipoxygenase inhibitor and an antihistamine, including astemizole, and Aslanian discloses other specific antihistimines, including norastemizole, the pending claims are obvious. This is not correct. Satoh merely discloses a broad genus of lipoxygenase inhibitors which can be used either alone, or in combination with other therapeutic agents, for the treatment of various inflammatory and allergic disorders. The mere fact that antihistamines are one of *many* "other therapeutic agents" listed in Satoh does not provide motivation for one skilled in the art to single out this class of compounds, much less to combine that reference with Aslanian, select norastemizole from a list of 38 other H_1 antagonists disclosed therein, and arrive at the claimed invention. Nowhere does the Examiner provide evidence of a suggestion in the prior art to combine Satoh and Aslanian in this way. At best, the Examiner is relying on an "obvious to try" standard, which is not the proper legal standard under 35 U.S.C. § 103.

See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

Applicant previously pointed out that Satoh cannot, and does not, render the pending claims obvious because Satoh does not place any limits as to the type of second therapeutic agent that can be combined with the lipoxygenase inhibitors it discloses (Response of Dec. 12, 2004, page 5). The Examiner rejects this contention, stating that Applicant's arguments "are not commensurate with the scope of the claims[1]." (Office Action, page 4). However, Applicant claims a specific therapeutic agent, norastemizole, in combination with leukotriene inhibitors, for the treatment of a specific disorder, allergic rhinitis. Therefore, Applicant submits that suggestion to combine each of these elements is completely absent in Satoh or Aslanian.

In addition, Applicant respectfully points out that the rejection is based on the Examiner's misunderstanding of legal principles, to the extent that the Examiner alleges that a "certain amount of picking and choosing amongst the disclosed species is permitted." (Office Action, page 5). This is flatly contrary to well settled legal principles. *See In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988)(examiner "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.").

Furthermore, the Examiner cites *In re Kerkhoven,* 626 F.2d 848, 205 U.S.P.Q. 1069 (C.C.P.A. 1980), for the proposition that it is generally considered *prima facie* obvious to combine two prior art compounds which have the same use in order to form a composition for that same use. Based on this principle, the Examiner rejects the pending claims merely because both norastemizole and leukotriene inhibitors are known anti-allergic agents. In *Kerkhoven*, the applicants claimed a process of making a detergent composition using two conventional detergents disclosed in the prior art. In contrast, the claimed invention is directed, in part, to the combination of two therapeutic agents. Combining two drugs for the treatment of a disorder in a human being is not analogous to combining detergents. For example, unfavorable drug-drug interactions are

[1] It is unclear why the Examiner considers the arguments not commensurate with the scope of the claims. Applicant's point was that Satoh, by not placing any limits as to what therapeutic agent may be combined with the lipoxygenase inhibitors it discloses, provides no suggestion or motivation whatsoever to those of ordinary skill in the art to select *any* of the second therapeutic agents it lists. The scope of the pending claims is irrelevant to these arguments.

well known to those skilled in the art, and such interactions are not often predictable.[2] By applying *Kerkhoven* to this case, the Examiner is oversimplifying the drug discovery process.

In this regard, antihistamines, specifically astemizole, are known to have adverse drug-drug interactions.[3] Many antihistamines and leukotriene inhibitors are known to interact with the same cytochrome P450 enzymes. *See The Merck Manual,* 17th ed. p. 564, 2584 (1999), a copy of which is submitted herewith. For example, both astemizole and zafirlukast (a lipoxygenase inhibitor) are known inhibitors of the same cytochrome P-450 enzyme CYP3A4. *Id. The Merck Manual* cautions the use of astemizole with any drug that inhibits these hepatic enzymes. *Id.* at 2583-84. Because norastemizole is structurally similar to astemizole, those skilled in the art have expected these compounds to exhibit similar drug-drug interactions. Thus, taking into account the potential for these unfavorable interactions, those of ordinary skill in the art would not have been motivated to combine norastemizole with a leukotriene inhibitor.

Because no suggestion or motivation to combine Satoh and Aslanian is provided, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn. *See ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984)("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.").

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[2] *See Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 10th ed., p. 54-56 (2001), a copy of which is submitted herewith.

[3] *See* Simons, F.E., *J. Allerg. Clin. Immunol.*, vol. 86, 995-999 (1990); and Paul W. Ament & Alex Paterson, *American Family Physician*, vol. 56, no. 1 (1997), a copy of which is also submitted herewith.

Conclusion

For at least the foregoing reasons, Applicant respectfully submits that all of the pending claims are allowable, and thus requests that their rejection be withdrawn.

No fee is believed due for this submission. Should any additional fees be required for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date August 26, 2005

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Cromolyn and **nedocromil** are given by inhalation prophylactically. They inhibit mediator release from inflammatory cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are useful in children and some adults only as maintenance therapy and have no place in treatment of an acute attack. They are the safest of all antiasthmatic drugs. Nedocromil has an unpleasant taste.

Leukotriene modifiers include montelukast and zafirlukast, selective competitive inhibitors of LTD_4 and LTE_4 receptors, and zileuton, a 5-lipoxygenase inhibitor. Although their role in treatment has not been established, these drugs, taken orally, are indicated for long-term control and prevention of symptoms in patients ≥ 12 yr (≥ 6 yr for montelukast) with mild persistent asthma. Zileuton may cause a dose-related increase in ALT or AST; montelukast does not. With zafirlukast, drug interactions mediated by cytochrome P-450 enzymes occur; in a few patients, Churg-Strauss syndrome has developed.

Education: The importance of patient education cannot be overemphasized: The more patients know about asthma—including what precipitates an attack, what drug to use when, how to use a spacer with a metered-dose inhaler, and how important early intervention with corticosteroids is when asthma worsens—the better they do.

Home peak flow monitoring combined with asthma education is extremely useful for patients with moderate to severe persistent asthma. When asthma is quiescent, one peak flow measurement in the morning suffices. If the patient's peak flow decreases to < 80% of *personal best*, then twice-a-day monitoring to assess diurnal variation is useful. Diurnal variation of > 20% indicates airway instability and the need to reevaluate the therapeutic regimen. Every patient should have a written action plan for day-to-day management, especially for management of acute attacks.

Day-to-Day Therapy

Appropriate drug use keeps most asthmatics out of the emergency department and hospital. Selection and the stepwise use of drugs are based on the severity of asthma (see TABLE 68–4).

Patients with mild intermittent asthma do not need daily medication. A short-acting β_2-agonist (eg, two inhalations of albuterol) is sufficient for acute symptoms. Using this drug more than two times a week may indicate the need for long-term control therapy. Regardless of the severity of the asthma, the frequent need for a β_2-agonist indicates that the asthma is not being controlled well.

For patients with mild persistent asthma, anti-inflammatory therapy—as an inhaled corticosteroid in low doses or as inhaled cromolyn or nedocromil—is indicated. Particularly in children, cromolyn is often tried before inhaled corticosteroids. Alternatively, extended-release theophylline can be given in a dose sufficient to produce a serum level of 10 to 15 μg/mL (56 to 83 μmol/L); dose varies by age and weight (usually 300 mg po bid in adults). Montelukast 5 mg (for patients 6 to 14 yr) or 10 mg (for adults) once daily in the evening or zafirlukast 20 mg bid 1 h before or 2 h after meals or zileuton 600 mg/day qid (for patients > 12 yr) may be considered. For acute symptoms, a short-acting β_2-agonist (eg, two inhalations of albuterol) may be used. The increasing need for inhaled β_2-agonists suggests that anti-inflammatory therapy should be increased.

Patients with moderate persistent asthma should be treated with an inhaled corticosteroid in a dose adjusted according to their response. The addition of a long-acting inhaled β_2-agonist (salmeterol) is useful for patients with nocturnal asthma and often lowers the inhaled corticosteroid dosage. An extended-release β_2-agonist oral formulation or extended-release theophylline may be substituted for the long-acting inhaled β_2-agonist, but each is associated with more side effects, especially in older persons.

A minority of asthmatics have severe persistent asthma; they often need several drugs in high doses. They should receive high-dose anti-inflammatory therapy with an inhaled corticosteroid (always using a spacer), a long-acting β_2-agonist—either an inhaled β_2-agonist with prolonged activity (such as salmeterol) or extended-release β_2-agonist tablets—and extended-release theophylline or a leukotriene modifier. Severely affected patients may require systemic corticosteroids; an alternate-day regimen helps minimize the adverse effects associated with a daily corticosteroid regimen. Once an inhaled corticosteroid optimally controls asthma, its dose should be tapered to the minimum required to maintain control. A short-acting inhaled β_2-agonist is needed for relief of acute symptoms.

TABLE 68-

*Step	Disease Severity	
1	Mild intermittent	None
2	Mild persistent	Daily Inh c s If n c ii a ii o c n
3	Moderate persistent	Daily Inh: Lon a o e:
4	Severe persistent	Daily Inh: o Lon ac ag th Oral

*Choice of treatment depe stepped up after the patient' reviewed. **Step-down:** Treatr down in treatment may be tri †Preferred treatments.

Treatment of an Acut

Acute asthma attack I), moderate (stage II), respiratory failure (sta

In stage I or II, treated with an aeroso (eg, albuterol nebulize mg/mL) nebulized by adults with acute asthr as effective given by a r with a spacer as by co zation. Alternatively, e given subcutaneously peated once or twice Terbutaline given subc

least 1/2 h before the first food, beverage, or drug of the day is taken.

Food may significantly alter the activity of theophylline in controlled-release but not immediate-release formulations. Taking a controlled-release formulation < 1 h before a high-fat meal significantly increases theophylline absorption and peak serum concentration vs. taking it in the fasting state.

Altered Distribution

Drugs may be displaced from protein-binding sites when two protein-bound drugs are given concurrently, especially if they can bind to the same sites on the protein molecule (competitive displacement). An equilibrium exists between bound (inactive) and unbound (active) drug fractions. As unbound drug is metabolized and excreted, bound drug is gradually released, maintaining equilibrium and pharmacologic response. The risk of interactions from protein displacement is significant primarily with drugs that are highly protein-bound (> 90%) and that have a small apparent volume of distribution; interactions tend to occur during the first few days of concurrent therapy.

Valproic acid reportedly displaces phenytoin from protein-binding sites and may also inhibit the metabolism of phenytoin. In some patients taking the two drugs, unbound phenytoin concentrations increase significantly, causing more adverse reactions, even when the total phenytoin serum concentrations are within the usual therapeutic range. Conversely, phenytoin may decrease valproic acid serum concentrations. Combination therapy with these drugs should be closely monitored, with dosage adjusted as needed.

Acidic drugs generally bind to serum albumin, and basic drugs to α_1-acid glycoprotein (see Binding in Ch. 298).

Altered Metabolism

(See also TABLE 301–1 and Pathways of Metabolism in Ch. 298.)

Stimulated metabolism: One drug may increase the activity of hepatic enzymes (enzyme induction) involved in the metabolism of another drug; eg, phenobarbital increases the metabolism of warfarin, decreasing its anticoagulant action. The warfarin dose must be increased to compensate, but if phenobarbital is discontinued, the warfarin dose must be decreased to avoid potentially dangerous toxicity. The use of a nonbarbiturate sedative (eg, a benzodiazepine) avoids the problem. Phenobarbital also increases the metabolism of other drugs (eg, steroid hormones). Other barbiturates and such drugs as carbamazepine, phenytoin, rifabutin, and rifampin also cause enzyme induction. Heavy smoking may decrease the efficacy of such drugs as chlorpromazine, diazepam, propoxyphene, and theophylline because polycyclic hydrocarbons in cigarette smoke increase the hepatic metabolism rate via enzyme induction.

Pyridoxine accelerates the decarboxylation of levodopa to its active metabolite, dopamine, in peripheral tissues. Unlike levodopa, dopamine cannot cross the blood-brain barrier to produce an antiparkinsonian effect. Giving carbidopa (a decarboxylase inhibitor) with levodopa prevents pyridoxine from interfering with levodopa's action.

Inhibited metabolism: One drug may inhibit the metabolism of another, possibly prolonging and increasing the action of the latter. For example, allopurinol reduces uric acid production by inhibiting the enzyme xanthine oxidase, which metabolizes such potentially toxic drugs as mercaptopurine and azathioprine. Inhibition of xanthine oxidase can markedly increase the effect of such drugs. Therefore, when allopurinol is given concurrently, the mercaptopurine or azathioprine dose should be reduced to about 1/3 to 1/4 the usual dose.

Cimetidine inhibits oxidative metabolic pathways and can increase the action of drugs metabolized via these pathways (eg, carbamazepine, phenytoin, theophylline, warfarin, most benzodiazepines [including diazepam]). Cimetidine does not affect the action of the benzodiazepines lorazepam, oxazepam, and temazepam, which undergo glucuronide conjugation. Ranitidine has less affinity for hepatic oxidative enzymes than does cimetidine, making clinically significant interactions with ranitidine less likely. Famotidine and nizatidine tend not to inhibit oxidative metabolic pathways and are unlikely to interact with other drugs via this mechanism.

Elevated serum concentrations of astemizole or cisapride can cause serious cardiovascular reactions (eg, torsades de pointes and other ventricular arrhythmias). Because

these drugs are extensively metabolized by hepatic cytochrome P-450 enzymes, their serum concentrations may increase when these enzymes are inhibited by such drugs as certain antidepressants (eg, nefazodone), clarithromycin, erythromycin, itraconazole, ketoconazole, and troleandomycin, increasing the risk of toxicity. Consequently, concurrent use of astemizole or cisapride with the above-mentioned and certain other drugs is contraindicated. Caution must be used when astemizole or cisapride is used concurrently with any drug that inhibits hepatic enzymes. The nonsedating antihistamines loratadine and fexofenadine have not been associated with serious cardiovascular reactions.

Ritonavir, a potent inhibitor of certain hepatic cytochrome P-450 enzymes, may markedly increase the serum concentrations of drugs metabolized by these enzymes (eg, antiarrhythmics, astemizole, most benzodiazepines, cisapride). Such drugs must not be used concurrently with ritonavir. Ritonavir also interacts with many other drugs, and concurrent use must be closely monitored, with dosage adjusted as needed.

Erythromycin reportedly inhibits the hepatic metabolism of such drugs as carbamazepine and theophylline, thereby increasing their effects. The fluoroquinolones ciprofloxacin, enoxacin, and grepafloxacin may markedly increase the activity of theophylline, presumably by the same mechanism.

Grapefruit juice inhibits CYP3A4, a cytochrome P-450 enzyme, and thereby increases the bioavailability of certain drugs (eg, felodipine) and increases their effect.

Altered Urinary Excretion

Altered urinary pH: Urinary pH influences the ionization of weak acids and bases, thus affecting their reabsorption and excretion. An un-ionized drug more readily diffuses from glomerular filtrate into blood. More of an acidic drug is un-ionized in acid urine than in alkaline urine, in which an acidic drug exists primarily as an ionized salt. Thus, more of an acidic drug (eg, a salicylate) diffuses back into blood from acid urine, resulting in prolonged and perhaps intensified activity. This effect is more likely among patients taking large doses of salicylates (eg, for arthritis). The effects are opposite for a basic drug (eg, dextroamphetamine). In one study, 54.5% of a dose of dextroamphetamine was excreted within 16 h when the urinary pH was maintained at about 5, compared with 2.9% when the pH was maintained at about 8.

Altered active transport: Probenecid increases the serum concentration and prolongs the activity of penicillin derivatives, primarily by blocking their tubular secretion. Such combinations have been used to therapeutic advantage.

When digoxin is given with quinidine, serum concentrations of digoxin are significantly higher than when it is given alone. Quinidine appears to reduce the renal clearance of digoxin, although nonrenal mechanisms are probably also involved.

Several NSAIDs reportedly increase the activity and toxicity of methotrexate. Fatal methotrexate toxicity has been reported in patients taking ketoprofen. Ketoprofen may inhibit active renal tubular secretion of methotrexate, but other mechanisms probably also contribute to increased serum methotrexate concentrations. Most of the patients who died were taking high doses of methotrexate for neoplastic disorders; however, caution is also needed when patients are given lower doses, particularly since low doses of methotrexate are being increasingly used for patients with rheumatoid arthritis who are also taking an NSAID.

PRINCIPLES OF MANAGEMENT

The following principles are important:

- Clinically significant interactions are most likely to occur between drugs that have potent effects, a narrow safety margin, and a steep dose-response curve (eg, cytotoxic, antihypertensive, and hypoglycemic drugs; digoxin; warfarin).
- A drug interaction may be difficult to distinguish from pathophysiologic factors affecting the response to therapy.
- Expected interactions may not occur; individual factors, such as dose and patient metabolism, are important determinants of interactions.
- When drug effects are closely monitored, an interaction usually does not result in significant adverse effects, but a change of dosage or the use of other drugs required.
- Displacing a drug from its protein sites alters the relationship betw and unbound drug, complicating cal interpretation of total drug c tions in the blood. When a highl displaceable drug is taken with a can displace it, total serum drug trations do not have the same m when such drugs are not taken rently. This fact is important be rum concentrations are often use treatment of patients taking vario

The incidence and clinical conse of drug interactions can be minimiz eral ways. The prescriber should k patient's total drug intake, includi prescribed by others and all OTC d few drugs in as low doses for as sh as needed should be prescribed. Th wanted and unwanted, of all dr should be determined, because thes usually include the spectrum of dr actions. If possible, drugs with a do that allows a considerable margin should be used. The patient shoul served and monitored for drug effe ticularly after a change in therapy; teractions (eg, metabolic effects d on enzyme induction) take ≥ 1 wk t Drug interactions should be consid possible cause of any unanticipat lems. When unexpected clinical re occur, serum concentrations of dru taken should be measured if poss literature or an expert in drug inte should be consulted; and the dose s adjusted until the desired effect is o If dose adjustment fails, the drug s replaced by one that does not inter other drugs being taken.

PLACEBOS

Presumably inactive substances controlled studies for comparis presumably active drugs or presc relieve symptoms or meet a pati mands for treatment.

Placebos may be any therapeutic ver (including surgical and psycholo niques), but this discussion is lin drugs (in all forms—eg, oral, parente ical).

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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of including women in early clinical trials, and the previous guidelines were revised to allow the participation of women in all phases of drug development. It is expected that at the time of drug approval, the database will be sufficiently complete to allow a rational assessment of the pharmacokinetic, pharmacodynamic, and safety issues in each sex (Sherman *et al.*, 1995; Harris *et al.*, 1995).

Drug–Drug Interactions. The use of several drugs often is essential to obtain a desired therapeutic objective or to treat coexisting diseases. Examples abound, and the choice of drugs to be employed concurrently can be based on sound pharmacological principles. In the treatment of hypertension, a single drug is effective in only a modest percentage of patients. In the treatment of heart failure, the concurrent use of a diuretic with a vasodilator and/or a cardiac glycoside often is essential to achieve an adequate cardiac output and to keep the patient free from edema. Multiple-drug therapy is the norm in cancer chemotherapy and for the treatment of certain infectious diseases. The goals in these cases usually are to improve therapeutic effectiveness and to delay the emergence of malignant cells or of microorganisms that are resistant to the effects of available drugs. When physicians use several drugs concurrently, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences of an interaction if they are adverse.

A *potential drug interaction* refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

The frequency of significant beneficial or adverse drug interactions is unknown. Surveys that include data obtained *in vitro*, in animals, and in case reports tend to predict a frequency of interactions that is higher than actually occurs. While such reports have contributed to skepticism about the overall importance of drug interactions, there are potential interactions of definite clinical importance, and the physician must be alert to the possibility of their occurrence. Estimates of the incidence of clinical drug–drug interactions range from 3% to 5% in patients taking a few drugs to 20% in patients who are receiving 10 to 20 drugs. Because most hospitalized patients receive at least six drugs, the scope of the problem clearly is significant. The recent successful treatment of AIDS with multiple drugs, including several that have potent effects to alter the activity of drug-metabolizing enzymes, has heightened the public awareness of drug interactions. Recognition of beneficial effects and recognition and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed, an inclination to attribute unusual events to drugs rather than to disease, and adequate observation of the patient. Automated monitoring of prescription orders in the hospital or outpatient pharmacy may decrease the physician's need to memorize potential interactions. Nevertheless, knowledge of likely mechanisms of drug interactions is the only way the clinician can be prepared to analyze new findings systematically. It is incumbent upon the physician to be familiar with the basic principles of drug–drug interactions in planning a therapeutic regimen. Such reactions are discussed for individual drugs throughout this textbook.

Interactions may be either pharmacokinetic (alteration of the absorption, distribution, or elimination of one drug by another) or pharmacodynamic (*e.g.*, interactions between agonists and antagonists at drug receptors). The most important adverse drug–drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug–drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if undertreated.

Pharmacokinetic Drug–Drug Interactions. Drugs may interact at any point during their absorption, distribution, metabolism, or excretion; the result may be an increase or decrease in the concentration of drug at the site of action. As individuals vary in their rates of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but it can be very significant.

The delivery of drug into the circulation may be altered by physicochemical interactions that occur prior to absorption. For example, drugs may interact in an intravenous solution to produce an insoluble precipitate that may or may not be obvious. In the gut, drugs may chelate with metal ions or adsorb to medicinal resins. Thus, Ca^{2+} and other metallic cations contained in antacids are chelated by tetracycline, and the complex is not absorbed. Cholestyramine adsorbs and inhibits the absorption of thyroxine, cardiac glycosides, warfarin, corticosteroids, and probably other drugs. The rate and sometimes the extent of absorption can be affected by drugs that alter gastric motility, but this is usually of little clinical consequence. Interactions within the gut may be indirect and complex. Antibiotics that alter the gastrointestinal flora can reduce the rate of bacterial synthesis of vitamin K such that the effect of oral anticoagulants, which compete with vitamin K,

will be enhanced. If a drug is metabolized by the gastrointestinal microorganisms, antibiotic therapy may result in an increase in the absorption of the drug, as has been demonstrated for some patients receiving digoxin (Lindenbaum *et al.*, 1981).

Recently, it has become evident that a number of drugs are substrates for various promiscuous transport systems that are present in many cells. P-glycoprotein (PGP) is the best studied of these systems, but many other systems are being discovered, such as the family of organic anion transporter systems. PGP is present in intestinal cells, renal tubular cells, biliary canalicular cells, and cells making up the blood-brain barrier. In the gut, PGP pumps drug into the lumen and thereby limits absorption. In the blood-brain barrier, PGP eliminates drug from the central nervous system (CNS), thus altering drug distribution. In the liver and kidney, PGP transports drug into the biliary canalicula and tubular lumen, thereby enhancing drug elimination. Inhibition of PGP therefore can alter the absorption, distribution, and elimination of drugs and is a topic of much current investigation. Cyclosporin A, quinidine, verapamil, itraconazole, and clarithromycin are examples of drugs that can inhibit PGP, whereas rifampin apparently can induce PGP. It is curious that inhibitors and inducers of CYP3A4 often appear to have similar effects on PGP, although this is not always true (Kim *et al.*, 1999). Much as there has been an explosion of information in the past decade about the CYP drug-metabolizing enzymes, the next decade promises a rich yield of information on PGP and similar transport systems.

Many drugs are extensively bound to plasma albumin (acidic drugs) or α_1-acid glycoprotein (basic drugs). In general, only unbound drug is free to exert an effect or to be distributed to the tissues. Thus, displacement of one drug from its binding site by another might be expected to result in a change in drug effects. Although such binding/displacement interactions occur, they are rarely of clinical significance. This is because the displaced drug distributes rapidly into the tissues: the larger the apparent volume of distribution of the drug, the less is the rise in the concentration of free drug in the plasma. Furthermore, following the displacement, more free drug is available for metabolism and excretion. Thus, the body's clearance processes eventually reduce the free drug concentration to that which existed prior to the drug displacement interaction. As a result, the effect of such an interaction is usually small, transient, and frequently unrecognized. However, the relationship of free drug to the total (bound plus free) drug is changed, and the interpretation of plasma drug assays that measure total drug concentration must be altered.

A few drugs are actively transported to their site of action. For instance, the antihypertensive drugs *guanethidine* and *guanadrel* inhibit sympathetic nervous system function after being transported into adrenergic neurons by the norepinephrine-uptake mechanism. Inhibition of this neuronal uptake system by tricyclic antidepressants and some sympathomimetic amines will inhibit the sympathetic blockade and reduce the antihypertensive effects of guanethidine and guanadrel. More drugs may be transported away from their site of action by PGP or other transporters. For example, cancer chemotherapy may be limited by transport of anticancer drugs out of tumor cells by PGP. Attempts have been made to block PGP in order to enhance chemotherapy, thus making use of a drug–drug interaction to enhance clinical efficacy (Krishan *et al.*, 1997).

Interactions involving drug metabolism can increase or decrease the amount of drug available for action by inhibition or induction of metabolism, respectively (*see also* Chapter 1). Interactions may occur among administered drugs or between drugs and dietary substances [*e.g.*, grapefruit juice (a CYP3A4 inhibitor)], herbal remedies [*e.g.*, St. John's wort (a CYP3A inducer); *see* Fugh-Berman, 2000], or other chemicals [*e.g.*, alcohol; other organic solvents (CYP2E1 inducers); cigarette smoke; polychlorinated biphenyls (CYP1A2 inducers)]. The effects of enzyme induction or inhibition are most obvious when drugs are given orally, because all of the absorbed compound must pass through the liver prior to reaching the systemic circulation. Additionally, the intestinal mucosa contains substantial amounts of CYP3A4, which can metabolize some drugs before they reach the portal circulation. Therefore, even for drugs that have a systemic clearance that is mainly dependent on hepatic blood flow (*e.g.*, propranolol), the amount of drug that escapes metabolism on the first pass will be influenced by enzyme induction or inhibition. Examples of drugs that are affected by enzyme inducers are oral anticoagulants, quinidine, corticosteroids, low-dose estrogen contraceptives, theophylline, mexiletine, methadone, HIV protease inhibitors, and some β-adrenergic blocking agents. Knowledge of the specific pathways of metabolism of a drug and of the molecular mechanisms of enzyme induction can help in planning studies of possible drug interactions, and preclinical drug development commonly includes studies to determine pathways of drug metabolism (Yuan *et al.*, 1999). Thus, if a compound is found to be metabolized by CYP3A4 in *in vitro* studies, the potential for clinically significant interactions can be focused on studies with commonly used drugs that can either inhibit (*e.g.*, ketoconazole) or induce (*e.g.*, rifampin) this enzyme. Probes for the evaluation of potential drug–drug interactions by the different CYP isoforms in human beings are being developed (*e.g.*, midazolam or erythromycin for CYP3A and dextromethorphan for CYP2D6). The example of arrhythmias triggered by a combination of terfenadine (which has been withdrawn from the market) and ketoconazole highlights the need for such studies in early drug development. In this interaction, ketoconazole inhibits the metabolism of terfenadine (by CYP3A4) to its active metabolite, resulting in high concentrations of unmetabolized terfenadine, which is toxic (Peck, 1993).

The ability of one drug to inhibit the renal excretion of another is dependent on an interaction at active transport sites. Many of the reported interactions occur at the anion transport site, where, for example, probenecid inhibits the excretion of penicillin to cause the desirable effects of elevated plasma concentrations of the antibiotic and a longer half-life. Similarly, the renal elimination of methotrexate is inhibited by probenecid, salicylates, and phenylbutazone, but in this case methotrexate toxicity may result from the interaction. Interactions at the transport site for basic drugs include the inhibition of excretion of procainamide by cimetidine and amiodarone. An interaction at renal tubular PGP causes inhibition of the excretion of digoxin by quinidine, verapamil, and amiodarone. Finally, the excretion of Li^+ can be affected by drugs that alter the ability of the proximal renal tubule to reabsorb Na^+. Thus, clearance of Li^+ is reduced and concentrations of Li^+ in plasma are increased by diuretics that cause volume depletion and by nonsteroidal anti-inflammatory drugs that enhance proximal tubular reabsorption of Na^+.

Pharmacodynamic Drug–Drug Interactions. There are numerous examples of drugs that interact at a common receptor site or that have additive or inhibitory effects due to actions at different sites in an organ. Such interactions are described throughout this textbook. Frequently overlooked is the multiplicity of effects of many drugs. Thus, phenothiazines are effective α-adrenergic antagonists; many antihistamines and tricyclic antidepressants are potent antagonists at muscarinic receptors. These "minor" actions of drugs may be the cause of drug interactions.

Other interactions of an apparently pharmacodynamic nature are poorly understood or are mediated indirectly. Halogenated hydrocarbons, including many general anesthetics, sensitize the myocardium to the arrhythmogenic actions of catecholamines. This effect may result from an action on the pathway that leads from adrenergic receptor to effector, but the details are unclear. The striking interaction between meperidine and monoamine oxidase inhibitors to produce seizures and hyperpyrexia may be related to excessive amounts of an excitatory neurotransmitter, but the mechanism has not been elucidated.

One drug may alter the normal internal milieu, thereby augmenting or diminishing the effect of another agent. A well-known example of such an interaction is the enhancement of the toxic effects of digoxin as a result of diuretic-induced hypokalemia.

Summary: Drug–Drug Interactions. Drug–drug interactions are only one of the many factors discussed in this chapter that can alter the patient's response to therapy. The major task of the physician is to determine if an interaction has occurred and the magnitude of its effect. When unexpected effects are seen, a drug interaction should be suspected. Careful drug histories are important, because patients may take over-the-counter drugs or herbal products, take drugs prescribed by another physician, or take drugs prescribed for another patient. Care must be exercised when major changes are made in a drug regimen, and drugs that are not necessary should be discontinued. When an interaction is discovered, the interacting drugs often may be used effectively with adjustment of dosage or other therapeutic modifications.

Fixed-Dose Combinations. The concomitant use of two or more drugs adds to the complexity of individualization of drug therapy. The dose of each drug should be adjusted to achieve optimal benefit. Thus, patient compliance is essential yet more difficult to achieve. To obviate the latter problem, many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient.

In the United States, a fixed-dose combination of drugs is considered a "new drug" and as such must be approved by the FDA before it can be marketed, even though the individual drugs are available for concurrent use. For such drugs to be approved, they must meet certain conditions. The two drugs must act to achieve a better therapeutic response than either drug alone, so that additional efficacy is achieved or the same effect is achieved with less toxicity (*e.g.*, many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (*e.g.*, a diuretic that promotes the urinary excretion of K^+ combined with a K^+-sparing diuretic).

Placebo Effects. The net effect of drug therapy is the sum of the pharmacological effects of the drug and the nonspecific placebo effects associated with the therapeutic effort. Although identified specifically with administration of an inert substance in the guise of medication, placebo effects are associated with the taking of any drug, active or inert.

Placebo effects result presumably from the physician–patient relationship, the significance of the therapeutic effort to the patient, or the mental set imparted by the therapeutic setting and by the physician. They vary significantly in different individuals and in any one patient at different times. Placebo effects commonly are manifested as alterations of mood, other subjective effects, and objective effects that are under autonomic or voluntary control. They may be favorable or unfavorable relative to the therapeutic objectives. Exploited to advantage, placebo effects can significantly supplement pharmacological effects and can represent the difference between success and failure of therapy.

A placebo (in this context, better termed *dummy medication*) is an indispensable element of many controlled clinical trials. In contrast, a placebo has only a limited role in the routine practice of medicine. A supportive physician–patient relationship generally is preferable to the use of a placebo for promoting therapeutic benefits. Relief or lack of relief of symptoms upon administration of a placebo is not a reliable basis for determining whether the symptoms have a "psychogenic" or "somatic" origin.

Tolerance. Tolerance may be acquired to the effects of many drugs, especially the opioids, various CNS depressants, and organic nitrates. When this occurs, *cross-tolerance* may develop to the effects of pharmacologically related drugs, particularly those acting at the same receptor site, and drug dosage must be increased to maintain a given therapeutic effect. Since tolerance does not usually

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Recent advances in H_1-receptor antagonist treatment

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The second-generation H_1-receptor antagonists terfenadine, astemizole, loratadine, and cetirizine are important first-line drugs for the relief of symptoms in patients with allergic rhinoconjunctivitis or chronic urticaria and may eventually supplant the potentially sedating first-generation H_1-receptor antagonists in the treatment of these disorders. Terfenadine, astemizole, loratadine, and cetirizine produce an incidence of central nervous system and anticholinergic adverse effects similar to that produced by placebo. Our ability to use H_1-receptor antagonists optimally has been greatly enhanced by recent pharmacokinetic and pharmacodynamic studies of these medications. (J ALLERGY CLIN IMMUNOL 1990;86:995-9.)

In this article we discuss the four newer, relatively nonsedating H_1-receptor antagonists currently available for use in many countries: terfenadine, astemizole, loratadine, and cetirizine (Fig. 1). Although each of these medications is recommended for once-daily administration (terfenadine, twice-daily administration in the United States) in the treatment of seasonal or perennial allergic rhinitis or urticaria, there are in fact considerable differences in their pharmacokinetics and pharmacodynamics (Table I). Our understanding of these differences facilitates optimal use of these medications.[1]

Abbreviations used
H_1: Histamine type 1
CNS: Central nervous system

TERFENADINE

Terfenadine[2-4] is well absorbed when administered by mouth and undergoes extensive biotransformation in humans. Peak serum concentrations are low, usually around 1 to 2 ng/ml after a 60 mg dose. For this reason, the active human carboxylic acid metabolite of terfenadine, terfenadine metabolite I, is usually quantitated instead of the parent compound. Different half-life values for terfenadine metabolite I have been reported; it is currently thought to be approximately 17 hours in young adults. For 24-hour suppression of wheal and flare, a 120 mg dose is more effective than a 60 mg dose. The pharmacokinetics and pharmacodynamics of terfenadine do not change during long-term administration; tolerance to the antihistaminic effect of terfenadine does not occur (Fig. 2).

In manufacturers' recommended doses, terfenadine causes no higher incidence of dry mouth, other anticholinergic effects, or CNS effects than does a placebo. Terfenadine does not interact with or potentiate the effects of alcohol, diazepam, or other CNS-active medications. Severe adverse reactions have been ex-

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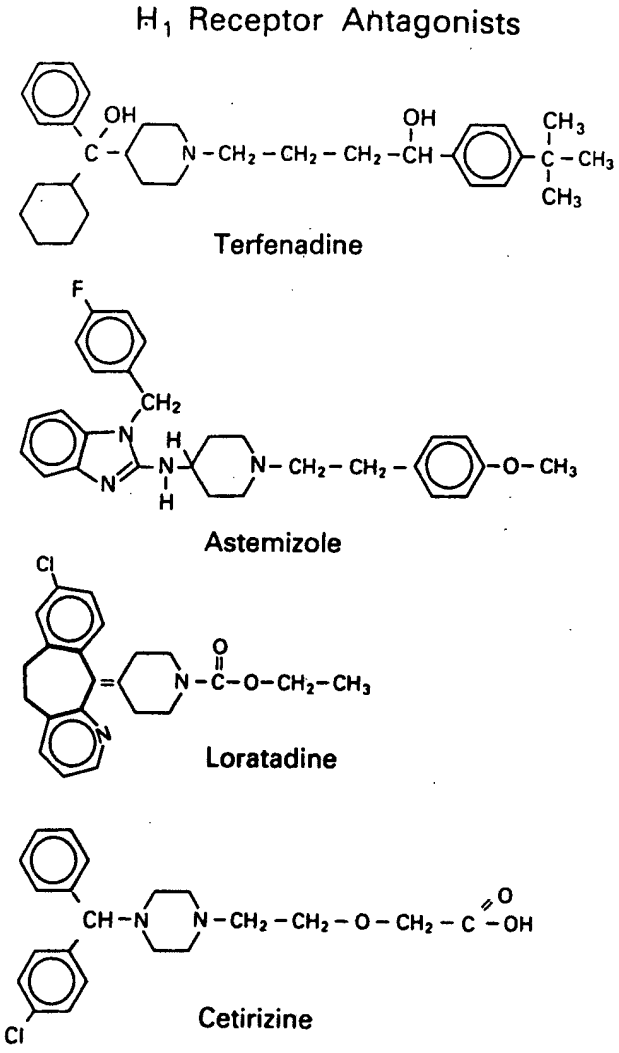

FIG. 1. Representative second-generation H_1-receptor antagonists.

tremely rare even in patients taking massive overdoses of terfenadine. For use in pregnancy, it is classified as a schedule C drug.

ASTEMIZOLE

Initially it was reported that absorption of astemizole from the gastrointestinal tract was decreased in the presence of food, but this is no longer believed to be true.[5] Astemizole seems to undergo extensive first-pass metabolism by the hepatic cytochrome P-450 system, and practically none of an oral dose is excreted in unchanged form in urine or feces. Desmethylastemizole is the main active human metabolite; norastemizole and 6-hydroxydesmethylastemizole are also produced. Peak serum concentrations of astemizole after a conventional 10 mg dose are extremely low, about 1 to 3 ng/ml. After a single 30 mg dose, the mean serum half-life of astemizole plus desmethylastemizole is 9½ days. Steady-state serum concentrations of 5 to 6 ng/ml of astemizole plus hydroxylated metabolites are achieved after 4 to 6 weeks of daily administration, and apparently further accumulation does not occur after this time.

A short course of astemizole, 10 mg daily, may significantly suppress the histamine-induced wheal and flare for weeks after its discontinuation. Even 14 weeks after discontinuation, some wheal-and-flare suppression may still be observed in some patients. Astemizole binds to peripheral H_1-receptor sites with far greater affinity than does any other existing H_1-receptor antagonist.

Astemizole does not induce any more sedation than does placebo. Some studies[5] have reported that it causes increased appetite and excess weight gain in some patients. A few patients taking astemizole, most of whom have admitted to taking overdoses of approximately 200 mg (20 times the recommended daily dose), have had torsade de pointes, syncope, and cardiac arrest. Astemizole does not interact with or enhance the effects of CNS suppression of alcohol, diazepam, or other CNS-active medications. No teratogenic effects have been observed in animal studies with astemizole. However, many physicians are concerned about its long serum half-life and believe that this medication should not be given to women who are contemplating child-bearing or who are pregnant or lactating.[1, 5-7]

LORATADINE

Like terfenadine and astemizole, loratadine results in extremely low maximum serum concentrations after a single 10 mg dose. It too is rapidly transformed into various metabolites, including descarboethoxyloratadine, which is active in humans, and is itself further metabolized. The serum half-life of loratadine in normal adults has been reported to be 7.8 to 11 hours; the serum half-life of the active metabolite is 17 to 24 hours. A single 10 mg dose of loratadine suppresses the histamine-induced wheal and flare for 12 to 24 hours. Doses of 20 mg or higher will significantly suppress the histamine-induced wheal and flare for 24 hours or more. The serum half-life of loratadine and its active metabolites may be slightly prolonged in some elderly patients. Subsensitivity to loratadine given daily for several months does not occur.[8-10]

Loratadine, 10 mg, does not cause any higher incidence of adverse effects (sedative or anticholinergic effects) than does placebo. Some sedation may occur with loratadine in doses of 40 mg/day. Loratadine

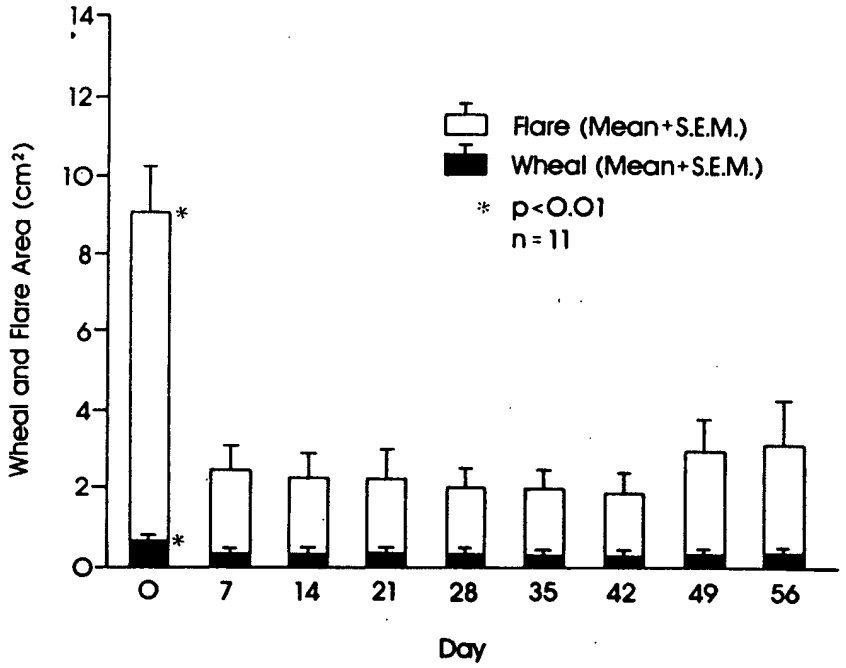

FIG. 2. Mean wheal-and-flare areas after intradermal injection of histamine phosphate, 1.0 mg/ml, at study entry (day 0) and 12 hours after a dose of terfenadine, 60 mg, on days 7, 14, 21, 28, 35, 42, 49, and 56. Subjects were ingesting terfenadine, 60 mg, twice a day regularly throughout the 56-day study. Wheal-and-flare areas did not differ significantly on days 7, 14, 21, 28, 35, 42, 49, or 56 and remained significantly suppressed compared with pretreatment wheal-and-flare size. No evidence of subsensitivity to the effect of terfenadine was found during long-term treatment.

TABLE I. Pharmacokinetics and pharmacodynamics of new H_1-receptor antagonists

H_1-receptor antagonist	T_{max} (hr)	$t_{½}$ (in normal adults)	Wheal suppression (after single dose) (hr)
Cetirizine	0.9	7.4 hr	24
Loratadine*	1.0	7.8-11 hr	12-24
Terfenadine†	1.0	17 hr	12-24
Astemizole‡	3.0	9.5 days	Variable

$t_{½}$, Half-life; T_{max}, time of maximum concentration.
*Loratadine metabolite, $t_{½}$ = 17 to 24 hours.
†Terfenadine metabolite I, $t_{½}$ = 17 hours.
‡Astemizole plus desmethylastemizole metabolite.

does not appear to interact with or potentiate the effects of alcohol, although in this regard it has not been studied as extensively as terfenadine and astemizole. Loratadine has not caused teratogenic effects in animals. It is classified as a schedule C drug for use in pregnancy in humans. In single-dose studies, concentrations of loratadine in breast milk were parallel to concentrations of loratadine in serum.

CETIRIZINE

Cetirizine is the carboxylic acid metabolite of the first-generation H_1-receptor antagonist hydroxyzine and is only metabolized minimally further in humans. A single 10 mg dose of cetirizine in adults results in maximum serum concentrations of approximately 300 ng/ml. Within 72 hours of a single dose of cetirizine, 70% of the medication appears unchanged in the urine.

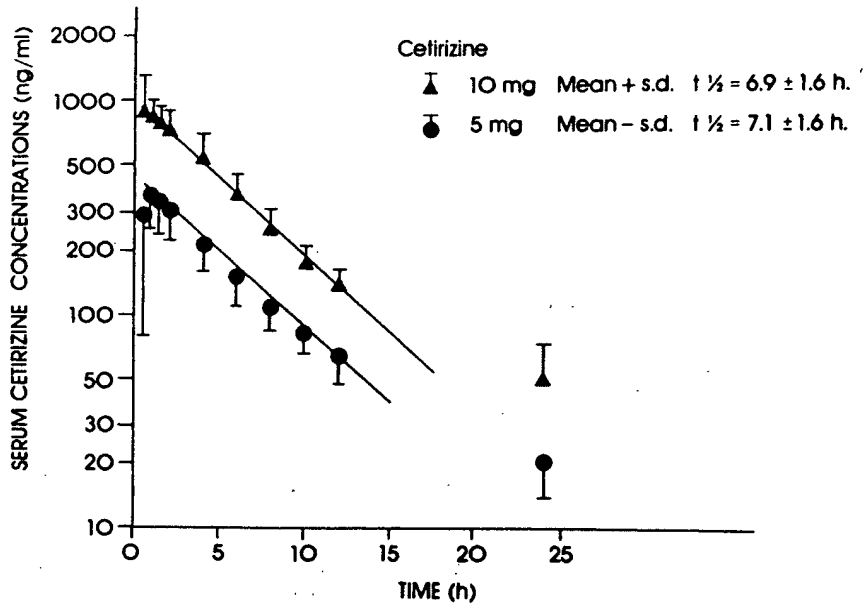

FIG. 3. Cetirizine concentration versus time plot: A double-blind, parallel group study of a single oral dose of cetirizine, 5 mg, in 10 children versus cetirizine, 10 mg, in 9 children.

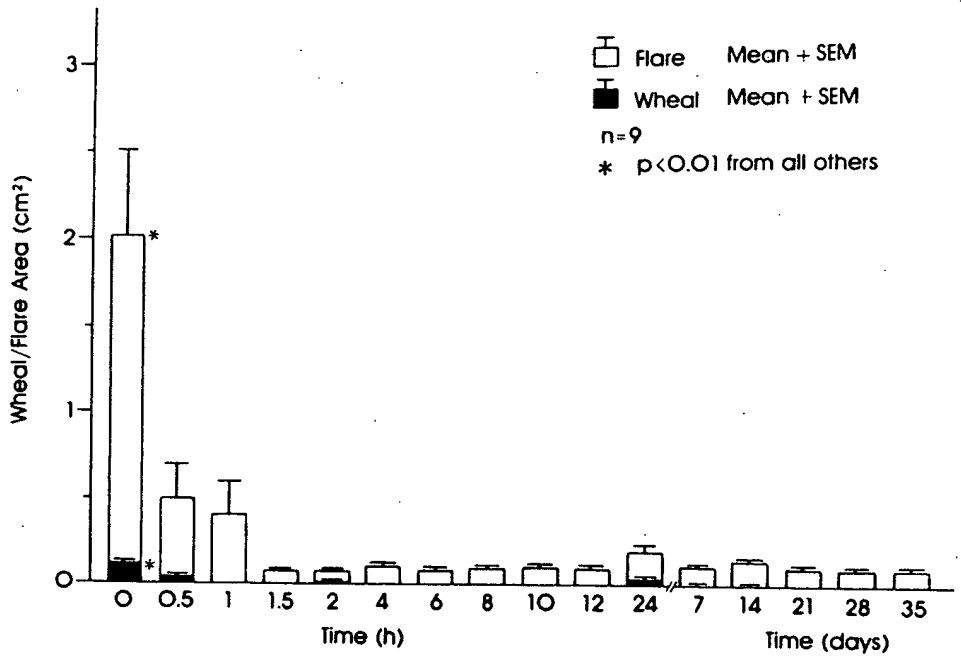

FIG. 4. Mean wheal-and-flare areas resulting from epicutaneous tests with histamine phosphate, 1 mg/ml, before and during the first 24 hours after a single dose of cetirizine, 10 mg, in nine children. Wheal-and-flare suppression 12 hours after administration on days 7, 14, 21, 28, and 35 during long-term once-daily administration with cetirizine, 10 mg, is also shown.

The serum half-life of cetirizine is approximately 7 hours in children (Fig. 3) and adults. It is slightly longer in elderly persons, and the half-life is approximately 18 hours in patients with renal failure. Cetirizine, 10 mg, has a prompt onset of action and effectively suppresses the wheal and flare for 24 hours. Subsensitivity to the antihistaminic effect of cetirizine does not occur during long-term administration (Fig. 4).

Cetirizine, 10 mg, produces a low incidence of anticholinergic and CNS adverse effects. Serious adverse effects have not been attributed to cetirizine.

Although cetirizine has been introduced into therapeutic use only recently, there has in fact been considerable worldwide experience with cetirizine during the past 40 years with the drug arising in vivo as a metabolite of hydroxyzine.[11-13]

SUMMARY

The second-generation H_1-receptor antagonists terfenadine, astemizole, loratadine, and cetirizine are relatively nonsedating and will be important first-line medications for use in patients with allergic rhinoconjunctivitis or urticaria. The pharmacokinetics and pharmacodynamics of these medications differ markedly, and physicians should understand these differences in order to use the medications optimally. These newer H_1-receptor antagonists are supplanting the first-generation H_1-receptor antagonists in the treatment of allergic rhinitis and chronic urticaria. However, first-generation H_1-receptor antagonists will continue to be used in patients for whom cost-effectiveness is an overriding factor, in young children who require liquid formulations, in patients requiring parenteral H_1-receptor antagonist formulations, and also in patients with atopic dermatitis, in whom the second-generation H_1-receptor antagonists have not proved to be superior to the first-generation H_1-receptor antagonists. However, in general the second-generation H_1-receptor antagonists represent a major advance in the symptomatic therapy of allergic disorders, and further interesting new developments in this area can be anticipated.

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Clinical Pharmacology

Drug Interactions with the Nonsedating Antihistamines

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The nonsedating antihistamines are frequently prescribed agents. Well-documented drug-drug interactions with two of these agents, terfenadine and astemizole, may result in serious adverse effects, including death, when they are prescribed along with macrolide antibiotics and/or the antifungal agents itraconazole or ketoconazole. Fexofenadine and loratadine appear to be the least likely nonsedating antihistamines to interact with other medications and to result in a life-threatening interaction. This article reviews the known drug-drug interactions involving nonsedating antihistamines and provides a basis from which the clinician can predict potential interactions.

Following the U.S. Food and Drug Administration's approval of terfenadine (Seldane) in 1985, serious ventricular arrhythmias, including torsades de pointes that occasionally resulted in death, have been associated with its use. Identified risk factors include concomitant use with macrolide antibiotics such as erythromycin, and antifungal agents, including itraconazole (Sporanox) and ketoconazole (Nizoral). Attempts to alert physicians to these potentially fatal drug-drug interactions have included "Dear Doctor" mailings and a black-box warning added to the prescribing information for both astemizole (Hismanal) and terfenadine.[1] Recently, the manufacturer of terfenadine has encouraged patients taking that drug to switch to fexofenadine (Allegra), which it also manufactures.

A review of Medicaid prescription claims showed that, despite educational attempts, physicians are often unaware of these drug-drug interactions; unfortunately, concomitant prescribing of potentially fatal drug combinations continues.[2] Pharmacists also sometimes overlook these serious drug-drug interactions. A recent report[3] showed that pharmacists failed to contact physicians 30 percent of the time when receiving prescriptions from patients taking both terfenadine and erythromycin and did not warn patients about signs or symptoms of the potential adverse effects one third of the time.

Currently, four nonsedating antihistamine agents have FDA approval: astemizole, fexofenadine, loratadine (Claritin) and terfenadine. In Claritin-D and Seldane-D, pseudoephedrine is combined with loratadine or terfenadine. All of these agents are frequently prescribed, accounting for more than 14 million prescriptions in 1996.[4] In addition, loratadine, loratadine plus pseudoephedrine, and terfenadine were the 18th, 41st and 86th most commonly prescribed medications in the United States in 1996.[4]

This article reviews the cytochrome P_{450} pathway implicated in drug-drug interactions with astemizole and terfenadine, the potential risks of combining nonsedating antihistamines with other medications, current drug-drug interaction data on fexofenadine and loratadine, and general concepts for evaluating potential drug-drug interactions with new medications.

Clinical Indications

Table 1 reviews current FDA-approved indications for the nonsedating antihistamines. A complete review of their mecha-

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TABLE 1

FDA-Approved Indications for the Newer Antihistamines

Agent	Adult indications*		Pediatric indications†	
	Seasonal allergic rhinitis	Chronic urticaria	Seasonal allergic rhinitis	
Astemizole (Hismanal)	X	X	—	—
Cetirizine (Zyrtec)	X	X	X	X
Fexofenadine (Allegra)	X	—	—	—
Loratadine (Claritin)	X	X	X	X
Terfenadine (Seldane)	X	—	—	—

*—*Over 12 years of age.*
†—*Over six years of age.*

nism of action, side effect profiles and clinical applications has been published previously.[5]

Cytochrome P_{450}

Knowledge of specific cytochrome pathways is clinically important in understanding potential drug-drug interactions. Cytochrome P_{450} is a group of enzymes responsible for metabolizing and detoxifying compounds. Primarily located in the liver and small intestine, they are also present in other tissues.[6,7] These enzymes are classified into families according to the similarity of their amino acid sequence.[8]

Agents that induce cytochrome P_{450} activity cause accelerated drug metabolism and decreased pharmacologic activity (unless the drug is transformed into an active metabolite, in which case metabolite-mediated effects may occur). Agents inhibiting cytochrome P_{450} activity cause reduced drug metabolism and an increased pharmacologic effect.

The clinical significance of a drug-drug interaction is difficult to assess solely from in vitro data, although agents inhibiting CYP2D6 (i.e., quinidine) will not interact with agents metabolized by CYP3A4 (i.e., astemizole, terfenadine). *Tables 2 and 3*[6-8] list known inhibitors and substrates (agents that compete for the metabolism) of cytochrome P_{450} enzymes.

Mechanism of Cardiotoxic Actions

Astemizole and terfenadine can cause the potentially fatal ventricular arrhythmia torsades de pointes when taken in an overdose or in recommended dosages when combined with certain interacting medications.[9,10] Terfenadine is a potent blocker of the myocardial potassium channel, which controls the QT interval.[9,10] Agents that

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TABLE 2

Inhibitors of Cytochrome P_{450} Enzymes

Enzyme inhibitor CYP2D6
Fluoxetine (Prozac)
Paroxetine (Paxil)
Quinidine
Sertraline (Zoloft)
Enzyme inhibitor CYP3A4
Cimetidine (Tagamet)
Clarithromycin (Biaxin)
Erythromycin
Fluvoxamine (Luvox)
Grapefruit juice
Itraconazole (Sporanox)
Ketoconazole (Nizoral)
Lovastatin (Mevacor)
Nafazedone (Serzone)
Norfluoxetine (Prozac metabolite)
Quinine
Troleandomycin (TAO)

Information from references 6 through 8.

block this channel may cause torsades de pointes. Risk factors for developing torsades de pointes while taking astemizole or terfenadine include (1) co-administration with agents that prolong the QT interval, (2) compromised hepatic function, (3) electrolyte alterations such as hypokalemia or hypomagnesemia, (4) congenital prolonged QT syndrome and (5) cardiac conditions such as bradycardia.[9] Syncope and cardiac arrest are other cardiovascular events resulting from use of astemizole and terfenadine.

Terfenadine is hepatically converted to an active metabolite, terfenadine carboxylate.[10] The cardiovascular effects of astemizole and terfenadine are solely due to the parent compound, not to the active metabolite.[9,10] The FDA recently approved fexofenadine, which is terfenadine carboxylate. This drug has not been reported to cause QT interval prolongation or other adverse cardiac effects.[9,10]

TABLE 3

Enzyme Substrates of Cytochrome P_{450} Enzymes

Enzyme substrate CYP2D6
Codeine
Metoprolol (Lopressor)
Paroxetine (Paxil)
Perphenazine (Trilafon)
Sertraline (Zoloft)
Venlafaxine (Effexor)
Enzyme substrate CYP3A4
Astemizole (Hismanal)
Cisapride (Propulsid)
Erythromycin
Terfenadine (Seldane)

NOTE: *When these drugs are taken in the presence of any of the inhibitor drugs in Table 2, their metabolism is decreased, and their side effect profile is potentially increased.*

Information from references 6 through 8.

Drug Interaction Data

Both astemizole and terfenadine carry a "black box" warning in their product literature stating that use of these agents concomitantly with ketoconazole, itraconazole, quinine and macrolide antimicrobials, including erythromycin, clarithromycin (Biaxin) and troleandomycin (TAO), is contraindicated.[11,12] Concomitant use with these agents may result in adverse cardiovascular events, including QT interval prolongation, ventricular arrhythmia and torsades de pointes, and even death. Most drug-drug interaction data involve terfenadine; however, clinicians should consider extrapolating the drug-drug interaction data to include astemizole because of the similarity between the two drugs.

The product literature for loratadine and fexofenadine does not contain the "black box" drug interaction warning because clinically significant interactions have not been reported with these two agents.[13,14] It is important to review the metabolic pathway for any agent used concomitantly with astemizole or terfenadine to consider whether there might be an opportunity for a severe drug-drug interaction. Clinicians should be cautious about prescribing, along with astemizole or terfenadine, agents that inhibit hepatic

TABLE 4

Drugs Contraindicated or Not Recommended for Administration with Astemizole (Hismanal) or Terfenadine (Seldane)

Antifungal agents	Antimicrobial agents	Others
Ketoconazole (Nizoral)	Azithromycin (Zithromax)*†	Fluvoxamine (Luvox)†
Itraconazole (Sporanox)	Clarithromycin (Biaxin)	Nafazedone (Serzone)†
	Erythromycin	Quinine‡
	Troleandomycin (TAO)	

*—*Azithromycin, an azolide, is structurally different from the macrolides (erythromycin, clarithromycin and troleandomycin); one supporting study[15] demonstrates safe concurrent administration with terfenadine (Seldane).*
†—*Not a "black-box" warning in the product literature.*
‡—*Not a "black-box" warning in terfenadine product literature.*

CYP3A4. *Table 4* lists drugs that are contraindicated for co-administration with astemizole or terfenadine. *Table 5* lists drugs that have demonstrated safe concomitant administration with astemizole, terfenadine, loratadine and fexofenadine.

AZALIDE INTERACTIONS

The combination of azithromycin (Zithromax), an azalide antibiotic, and terfenadine was evaluated for potential interaction in a 12-day pharmacokinetic study in 24 patients.[15] Terfenadine, given in a dosage of 60 mg twice daily on days 1 through 12, and azithromycin, administered in a five-day regimen of 500 mg on day 8 and 250 mg on days 9 through 12, did not result in increased serum levels of terfenadine or produce QT interval changes.[15] Although this information may suggest that azithromycin is a rational choice if treatment with an "erythromycin-like" drug is clinically necessary, clinicians must realize that azithromycin product labeling recommends against concomitant use (not a black-box warning, however) with astemizole and terfenadine, pending more complete interaction data.

TABLE 5

Agents Demonstrating Safe Concomitant Administration with Astemizole (Hismanal), Fexofenadine (Allegra), Loratadine (Claritin) or Terfenadine (Seldane)

Antifungal agents	Histamine H_2 antagonists
Fluconazole (Diflucan)	Cimetidine (Tagamet)
Terbinafine (Lamisil)	Famotidine (Pepcid)
Antidepressants	Nizatidine (Axid)
Paroxetine (Paxil)	Ranitidine (Zantac)
Sertraline (Zoloft)	
Tricyclics	

ANTIFUNGAL INTERACTIONS

The antifungal agent terbinafine (Lamisil) was administered with terfenadine to 18 healthy volunteers.[16] This combination did not result in proarrhythmic effects or change the pharmacokinetics of terfenadine or its metabolite. Therefore, terbinafine and terfenadine can probably be safely co-administered.[16]

Fluconazole (Diflucan), in a dosage of 200 mg once daily, when administered with terfenadine, in a dosage of 60 mg twice daily, resulted in a pharmacokinetic interaction. The serum concentration increased for the terfenadine carboxy metabolite, but there was no increase in parent terfenadine level (thus, no cardiotoxic potential). No pharmacodynamic interaction resulted because no electrocardiographic changes occurred, and no patients reported an adverse effect.[17]

ANTIHISTAMINE INTERACTIONS

Concurrent administration of terfenadine with the histamine H_2 antagonists cimetidine (Tagamet) and ranitidine (Zantac) appears to be safe. In a study[18] of 12 healthy volunteers, no clinically significant prolongation of the QT interval or accumulation of parent terfenadine occurred when the latter agent was given for six days concurrently with cimetidine or ranitidine. Famotidine (Pepcid) and nizatidine (Axid) do not inhibit cytochrome P_{450} and are also considered to be safe for concomitant administration.

SEROTONIN INHIBITOR INTERACTIONS

The selective serotonin reuptake inhibitors (SSRIs) are another frequently prescribed group of drugs. Fluoxetine (Prozac) is metabolized to norfluoxetine, which inhibits CYP3A4. A few case reports relate use of this agent and terfenadine with cardiac toxicity.[19]

In one report,[19] a patient developed asymptomatic QT interval prolongation after concurrent administration of fluoxetine (at 40 mg daily) and terfenadine (at 60 mg twice daily). The patient's electrocardiogram returned to normal seven days following discontinuation of terfenadine. The agents paroxetine (Paxil) and sertraline (Zoloft) inhibit CYP2D6 and, thus, should not interact adversely with astemizole or terfenadine.[7,8]

LORATADINE

In a study of 24 patients,[20] loratadine, in a dosage of 10 mg once daily for 10 days, plus erythromycin, 500 mg every eight hours, produced a two-fold increase in serum concentrations of parent loratadine and its metabolite. The safety profile did not change, no adverse effects were noted, and no QT interval changes were reported.

Cimetidine (Tagamet), administered to 24 patients in a dosage of 300 mg every six hours, with loratadine, in a dosage of 10 mg once daily for 10 days, produced a 103 percent increase in plasma concentration of loratadine, while the metabolite serum level was unchanged (personal communication: Kimberly DeFronzo, Schering-Plough Research Institute, July 1996). No clinically relevant side effects or QT interval changes occurred despite the increased loratadine serum concentration.

In another study, 50 patients received loratadine in a dosage of 40 mg once daily (four times the recommended dosage) for 90 days, without any reported adverse effects such as drowsiness or changes in the PR, QRS or QTc intervals.[21] Despite increased serum levels of parent loratadine when co-administered with cytochrome P_{450} inhibitors, these fluctuations did not cause conduction changes in the myocardium. Although the clinical studies may be limited by small sample size, these data suggest torsades de pointes may not be a "class effect" of all the nonsedating antihistamines. Thus, each agent should be individually evaluated for its cardiac effects.

FEXOFENADINE

Specific data about drug-drug interactions with fexofenadine, the carboxy metabolite of terfenadine, are limited to erythromycin and ketoconazole; in these instances, peak serum concentrations increased by 82 percent and 135 percent, respectively.[14] No increase in adverse effects, no cardiovascular changes and no QT interval prolongation occurred despite the increased serum levels.[14] Fexofenadine appears to be as safe as loratadine in co-administration. Fexofenadine requires twice-daily dosing. No liquid formulation of this agent or combination product containing a decongestant is currently available.

CETIRIZINE

Cetirizine (Zyrtec), the metabolite of hydroxyzine, is marketed as a "less-sedating" antihistamine, a classification that is not actually used by the FDA. Cetirizine is not labeled as a nonsedating antihistamine because it produces a higher incidence of somnolence and fatigue than placebo.[22] Drug-drug interaction data evaluating cetirizine reveal no clinically significant changes in serum levels when the agent is combined with the medications summarized below (personal communication: John D. Ostrosky, Pfizer Inc., September 1996).[23,24]

In 42 patients, cetirizine, in a dosage of 20 mg per day (twice the FDA-approved dosage) for 11 days, combined with a standard five-day regimen of azithromycin, caused no side effects or QT interval prolongation.[23] In 16 patients, erythromycin, in a dosage of 500 mg three times daily, ad-

Nonsedating Antihistamines

TABLE 6

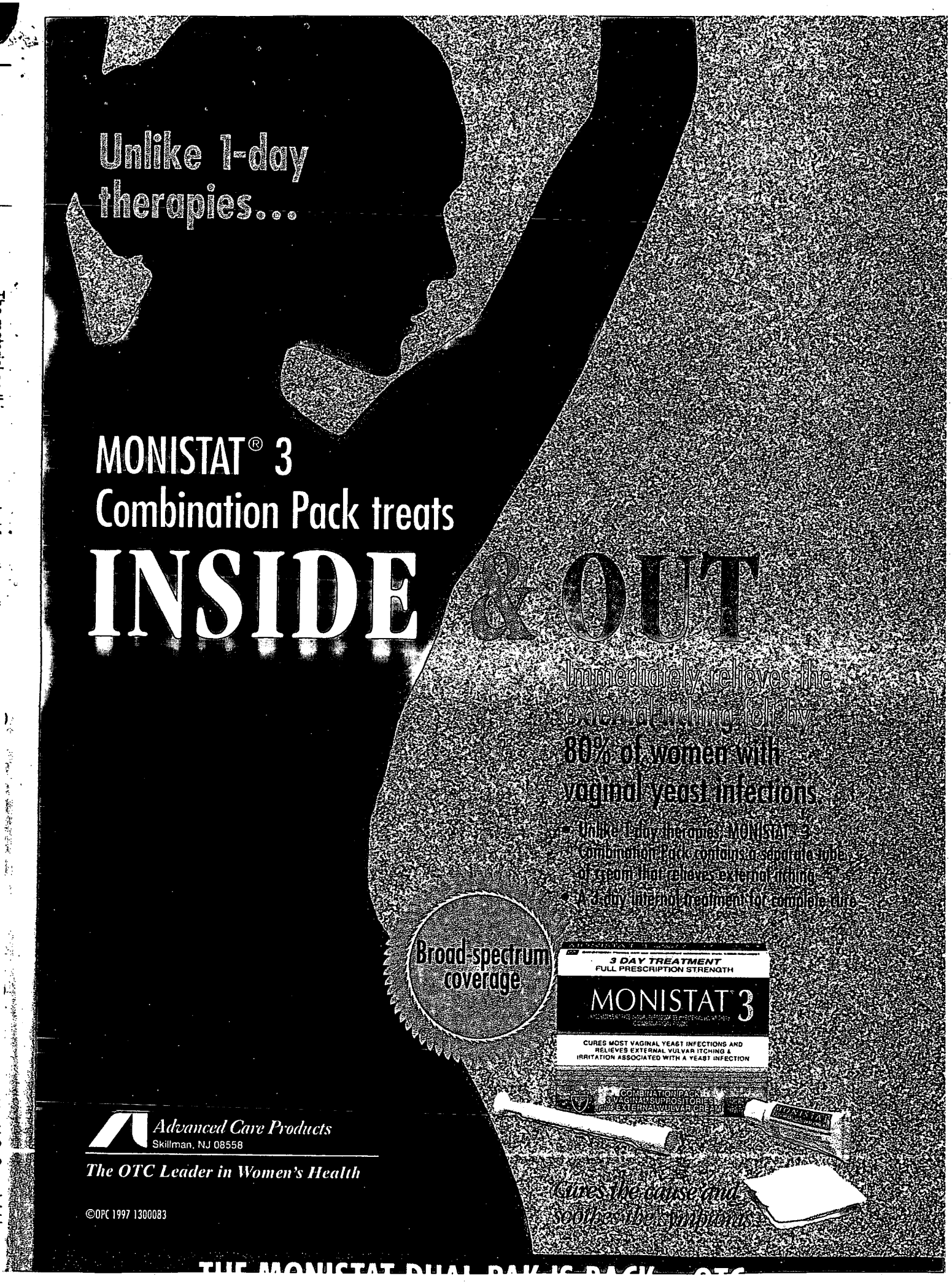
Dosage Recommendations and Monthly Cost for Selected Antihistamines

	Recommended dosage				
Agent	*Adults*	*Pediatric (>6 years of age)*	*Pediatric (2 to 6 years of age)*	*Pediatric (<2 years of age)*	*Cost**
Astemizole (Hismanal)	10 mg daily	None	None	None	$58.00
Cetirizine (Zyrtec) tablets	5 to 10 mg daily	None	None	None	53.00
Cetirizine syrup	5 to 10 mg daily	5 to 10 mg daily	None	None	32.00
Chlorpheniramine maleate (Chlor-Trimeton)	4 mg every 4 to 6 hours	2 mg every 4 to 6 hours	1 mg every 4 to 6 hours	0.35 mg per kg per day in divided doses every 4 to 6 hours	15.00 (3.50‡)
Diphenhydramine (Benadryl)	25 to 50 mg every 6 to 8 hours	12.5 to 25 mg every 4 to 6 hours	6.25 mg every 4 to 6 hours	5 mg per kg per day in divided doses every 6 to 8 hours	10.00 (3.50‡)
Fexofenadine (Allegra)	60 mg twice daily	None	None	None	52.00
Hydroxyzine (Atarax)	25 mg three to four times daily	12.5 to 25 mg every 6 hours	0.5 mg per kg per day in divided doses every 6 hours	0.5 mg per kg per day in divided doses every 6 hours	78.00 (10.00‡)
Loratadine (Claritin)	10 mg daily	10 mg daily	None	None	58.00
Loratadine, 10 mg, plus pseudoephedrine, 240 mg (Claritin-D 24-hour)	1 tablet daily	None	None	None	70.00
Loratadine syrup, 10 mg per 10 mL	10 mL daily	10 mL daily	None	None	73.00
Loratadine, 5 mg, plus pseudoephedrine, 120 mg (Claritin-D 12-hour)	1 tablet every 12 hours	None	None	None	65.50
Terfenadine (Seldane)	60 mg two times daily	None	None	None	54.00 (53.00‡)
Terfenadine, 60 mg, plus pseudoephedrine, 120 mg (Seldane D)	1 tablet two times daily	None	None	None	63.50

*—*Estimated cost to the pharmacist for one month of therapy at the lowest adult dosage level based on average wholesale prices, rounded to the nearest half dollar, in Red book. Montvale, N.J.: Medical Economics Data, 1997. Pediatric costs will vary from adult costs because the dosages are different. Consumer cost will be higher depending on filling fee.*

†—*Over-the-counter.*

‡—*Average generic price.*



ministered with cetirizine, in a dosage of 20 mg daily for 10 days, did not cause any pharmacokinetic changes in cetirizine or prolong the QT interval.[24] The pharmacokinetics of cetirizine (e.g., half-life, area under the curve, peak serum concentration) did not significantly change with concomitant cimetidine administration, so the authors conclude that this combination is safe for co-administration.[24]

Dosage recommendations and monthly cost of selected antihistamines can be found in *Table 6*.

Final Comment

Because of the arrhythmogenic potential when astemizole and terfenadine are administered with other medications, the clinician should be cautious when prescribing these two agents.

A patient information handout on prescription antihistamines, written by the authors of this article, is provided on page 231.

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